amylase to produce a nucleic acid encoding a deletion, insertion, or substitution of one or more amino acids at a position corresponding to said structural part; and

(e) expressing the modified nucleic acid in a host cell to produce the variant alpha-amylase, wherein the variant has alpha-amylase activity and has one or more altered properties as compared to the first alpha-amylase.

C2 CONT

REMARKS

Entry of this amendment is respectfully requested.

Claims 71 and 72 were pending. In this response, claims 71 and 72 are amended for further clarity and new claims 73-75 are added. Support for the amendments and new claims can be found in the specification and claims as originally filed. For example, α-amylases having 80% homology to the polypeptide whose three-dimensional structure is described in the Appendix are disclosed at page 5, line 10. Host cells suitable for expression of variant α-amylases are disclosed, e.g., at page 43, line 15 - page 44, line 9. The interchangeability in the present method of three-dimensional structures obtained by X-ray crystallographic analysis and those obtained by modelling is disclosed in the specification at page 12, lines 2-6. No new matter is added. Accordingly, claims 71-75 are pending and at issue.

It is pointed out that the equivalence of "non-Termamyl-like" alpha-amylases and alpha-amylases "unrelated" to the parent alpha-amylases as defined in the present claims is supported in the specification at page 15, lines 11-17.

The Examiner has objected to the specification for informalities in the Brief Description of the drawings, which are corrected herewith.

Applicants thank the Examiner for the courtesies extended at an interview with the undersigned on January 11, 2000. This response incorporates the discussion at the interview.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 71 and 72 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner contends that obtaining X-ray crystallographic structures is unpredictable, and that it would require undue experimentation to obtain such structures from α-amylases that are 70% homologous to the polypeptide whose X-ray structure is

disclosed in the Appendix. This rejection is respectfully traversed.

The family of α-amylases designated "Termamyl-like" in the present specification, which have sequences at least 70% homologous to SEQ ID Nos: 2, 4, 6, or 13, are highly related structurally. It is believed therefore that Applicants' success in crystallizing a representative α-amylase reflects the operability of the invention encompassing the use of a crystal structure of any α-amylase that is at least 70% homologous to SEQ ID Nos: 2, 4, 6, or 13. This is supported by subsequent reported X-ray crystal structures, such as, e.g., by Machius et al., *J. Mol. Biol.* 246:545, 1995.

Nonetheless, to expedite prosecution, claims 71 and 72 have been amended to require that the X-ray crystal structure on which the parent α-amylase is modelled be that of a polypeptide at least 80% homologous to one of the disclosed "Termamyl-like" α-amylases. It is respectfully submitted that this close relationship provides a strong expectation of obtaining an X-ray crystal structure for use in the presently claimed method, and that this rejection has been overcome.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 71 and 72 have been rejected under 35 U.S.C. § 112, second paragraph, as indefinite, for the recitation of "expressing the modified nucleic acid". The Examiner contends that it is unclear where the nucleic acid is expressed.

In this response, claims 71 and 72 have been amended to specify the use of a host cell. It is respectfully submitted that this rejection has been overcome and should be withdrawn.

Claim 72 has been rejected as indefinite for the recitation of an "unrelated" α-amylase. This rejection is respectfully traversed.

The present specification describes in detail the relationship between the members of the "Termamyl-like" family of α-amylases and distinguishes this family from others, such as, e.g., the "Fungamyl-like" α-amylases. Thus, one of ordinary skill in the art, reading the present specification, would understand the metes and bounds of this claim. On this basis, it is respectfully submitted that this claim is definite and that the rejection should be withdrawn.

Rejection Under 35 U.S.C. § 103

Claim 72 has been rejected under 35 U.S.C. § 103(a) as unpatentable over MacGregor, *J. Prot. Chem.* 7, 399, 1988. The Examiner contends that MacGregor discloses methods for predicting α-amylase structure, in particular the relationship between the structure of *Bacillus* and *Aspergillus* amylases, and that it would have been obvious, based on MacGregor, to practice the steps of the present invention. This rejection is respectfully traversed.

As discussed in an interview with the inventors in relation to the parent case (U.S. Serial No. 08/600,908, now U.S. Patent No. 5,989,169), the useful (i.e., correct) structural information in MacGregor is limited to the central β-barrel structure and the structure of some of the surrounding α-helices. MacGregor incorrectly predicts the structures of regions believed to be important in mediating the altered properties recited in the present claims. Accordingly, prior to the present invention, one of ordinary skill in the art, based on MacGregor, could not have had any reasonable expectation of success at predictively mutating this family of α-amylases to achieve variants that exhibit altered properties. On this basis, it is respectfully submitted that the present claims are non-obvious over MacGregor and that this rejection should be withdrawn.

In view of the above amendments and remarks, it is believed that the claims are in condition for allowance, and a determination to that effect is earnestly solicited.

Respectfully submitted,

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Reza Green, Reg. No. 38,475
Novo Nordisk of North America, Inc.
405 Lexington Avenue, Suite 6400
New York, NY 10174-6401
(212) 867-0123

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